Supplementary Information

We present below a more detailed description of studies relating to the localization of brain GnRH neurons and GnRH1, GnRH receptors, gonadotropins, gonadotropin receptors, StAR, sex steroids, sex steroid receptors, kisspeptin and kisspeptin receptor (GPR54). This information was used in the spatial localization of the various components of the feedback axes in the model (Fig. 5).

i. GnRH Neurons and Neural GnRH1 Production: In addition to the known GnRH1-pathways (preoptico-terminal, preoptico-infundibular, periventricular), GnRH1-immunopositive processes are present in several major tracts and areas of the brain, including the medial and cortical amygdaloid complex, stria terminalis, stria medullaris thalami, fasciculus retroflexus, medial forebrain bundle, indusium griseum, stria longitudinalis medialis and lateralis, hippocampus, periaqueductal gray of the mesencephalon, and extracerebral regions, such as the lamina cribrosa, nervus terminalis and its associated ganglia (Merchenthaler et al. 1984; Tobet et al. 1996; Quanbeck et al. 1997; Kim et al. 1999; Reed et al. 2002). The short serum half-life of GnRH I (~2-3 min.) (Redding et al. 1973; Fauconnier et al. 1978) would support autocrine release of GnRH I within the brain, although it has been shown in rats that GnRH I can cross the BBB (Dvorska et al. 1992).

ii. GnRH Receptors: GnRHR1 initiates the release of gonadotropins from pituitary gonadotropes (Miller and Gibson 1994; Millar et al. 2004). GnRHR1 has been localized to extrapituitary areas of the rodent brain including the hippocampus, amygdala, entorhinal cortex and subiculum, with lower expression in the septum and frontal cortex, but is not greatly expressed in the hypothalamus (Reubi and Maurer 1984; Badr and Pelletier 1987; Haour et al. 1987; Reubi et al. 1987; Jennes et al. 1988; Leblanc et al. 1988; Badr et al. 1989; Ban et al. 1990; Thompson and Moss 1992; Crumeyrolle-Arias et al. 1994; Jennes et al. 1995; Jennes et al. 1996; Jennes et al. 1997; Pierpaoli and Lesnikov 1997; Lu et al. 1999; Granger et al. 2004). The density of GnRHR1 appears to be highest in the stratum oriens and stratum radiatum of the CA1-CA4 regions of Ammon's horn (Reubi et al. 1987; Leblanc et al. 1988). Studies using GnRH1 agonists have identified a high affinity-binding site (0.12–1.00 nM) in the hippocampus that compares closely with pituitary GnRHR1 (reviewed in Vadakkadath Meethal and Atwood 2005), suggesting an important role for GnRH1 in hippocampal function. We recently reported GnRHR1 expression on neurons of the hippocampus and cortex of the human brain, but not in the granular layer of the dentate gyrus or other neuronal cell types (Wilson et al. 2006).

iii. Gonadotropins: LH has been immunolocalized to the cytoplasm of neurons of the cerebral cortex and hippocampus of the human and rat brains (Hostetter et al. 1981; Emanuele et al. 1983; Bowen et al. 2002), and is found in cerebrospinal fluid (Bagshawe et al. 1968). The exact origin of extrapituitary intracellular LH is unclear. One possible explanation is that pyramidal neurons sequester LH from extracellular sources (e.g. blood). This is supported by the findings that pyramidal neuron LH is elevated approximately 2-fold in AD compared with age-matched control brains (Bowen et al. 2002), an increase that correlates with a 2-fold increase in serum LH at this time (Bowen et al. 2000; Hogervorst et al. 2001; Short et al. 2001). Another intriguing possibility is that aging neurons, like fetal and cancer cells, might be capable of synthesizing LH (Whitfield and Kourides 1985; Krichevsky et al. 1995; Yokotani et al. 1997). We recently demonstrated that GnRH1 induces LH expression by neuroblastoma cells and is present in primary rat neurons (Wilson et al. 2006). FSH has not been reported in the brain, however *FSH* mRNA is present in the adult rat brain (Allen Brain Atlas) and is expressed most prominently in the medulla, cerebellum, and pons, with significant expression in cerebral cortex, hippocampus, hypothalamus, the midbrain, pallidum, retrohippocampal region, and thalamus, and low levels of expression elsewhere.

iv. Gonadotropin Receptors: All neuronal cell types (neurons, astrocytes, glia) studied to date possess LH/hCG receptors (Zhang et al. 1994; Bukovsky et al. 2003; Bowen et al. 2004). Mature glycosylated and phosphorylated LH/hCG receptor (~92 kDa), immature full length LH/hCG receptor (59 kDa isoform) and minor variants that migrate at 48 and 68 kDa have been detected by immunoblot analyses in the cortex of young and aged individuals (Bowen et al. 2004). Likewise, LH/hCG receptor expression (mRNA and protein) has been detected in the adult rat brain with the highest density of LH/hCG receptors being found within the hippocampus (Lei and Rao 1994). The expression of neuronal LH/hCG receptors, and therefore receptor signaling, is modulated by both E_2 and LH (Bowen et al. 2004; Liu et al. 2007). Protein for FSHR has been difficult to detect in the brain, however *FSHR* mRNA is present throughout the rodent brain (Allen Brain Atlas) with the highest expression levels found in the

cerebellum, with significant expression, albeit ~10-20 fold less in most other regions including cerebral cortex, hippocampus, medulla, and the olfactory bulb.

v. StAR and steroidogenic enzymes: The expression of steroidogenic acute regulatory protein (StAR) and aromatase are three-fold higher in neurons of the CA3 than that of the CA1 region and in granule cells (Prange-Kiel et al. 2006). Steroidogenic enzymes required for NSS production are expressed in the brain (Barbaccia et al. 2001; Schumacher et al. 2004; Veiga et al. 2004). The biosynthesis of neurosteroids proceeds through cholesterol side-chain cleavage, and gives rise to 3β-OH-Δ5-compounds, such as P_5 and dehydroepiandrosterone (DHEA), their sulfates, P_4, and reduced metabolites such as the tetrahydroderivative of P_4, 3α-OH-5α-pregnane-20-one (3α,5α-THPROG). These steroids accumulate in the brain independently of the supply by peripheral endocrine glands. In rat, the CNS synthesizes P_5 and converts it into P_4 and some of its 5α-reduced metabolites, although different cell types perform different functions. Astrocytes can convert the neurosteroid P_5 into the steroid hormone P_4, 20α-dihydro-P_5, 5α-dihydro- P_4, and the neuromodulatory steroid 3α,5α-tetrahydro-P_4, whereas neurons lack the Δ5-3β-hydroxysteroid dehydrogenase isomerase activity (and cholesterol scc activity), necessary for the biosynthesis of P_4 (Kabbadj et al. 1993). Neurons can however convert P_5 into 20α-dihydro-P_5. Thus, there is likely considerable cross-talk between glia and neurons in the regulation of steroid production (Barbaccia 2004).

vi. Sex Steroids: Brain sex steroid concentrations are uneven across various regions of the brain and the dose-dependence of their response to a pharmacological challenge shows brain-regional differences as well (Compagnone and Mellon 2000; Barbaccia 2004). This is consistent with the distribution of steroidogenic enzymes in brain, which show not only a brain region, but also a cell-specific expression that may spatially and temporally determine the local concentrations of specific NSS, either produced *ex novo* or through metabolism of steroid precursors that reach the brain through blood. Please see above papers for more comprehensive information on the location of steroidogenic enzymes in the brain.

vi. Sex Steroid Receptors: Sex steroid receptors for estrogen receptor (ERα and ERβ), androgen receptor and progesterone receptor A and B (PRA and PRB), aside from being found in the hypothalamus and pituitary, are widely distributed in the brain with the highest concentrations being found in the limbic system (amygdala, cerebral cortex, midbrain central grey) and structures of the telencephalon (McEwen 1988; Sherwin 1999; Guerra-Araiza et al. 2001; Gao and Goldman-Rakic 2003; Nunez et al. 2003; Shima et al. 2003). Ultrastructural data reveals extranuclear ERα immunoreactivity within select dendritic spines on hippocampal principal cells, axons, axon terminals, and glial processes (McEwen 2002). It has been suggested that the presence of ER in dendrites is responsible for synapse formation in which filopodia from dendrites grow out to find new synaptic contacts (McEwen 2002). PRs have been identified in peripheral and central glial cells (Baulieu 1997). Estrogens, but not progestins, have been shown to induce the expression of PRA, but not PRB, in the hippocampus (Camacho-Arroyo et al. 1998; Alves et al. 2000) although there is no change in PR isoform content in the hippocampus during the estrous cycle (Behl 2002; Blaustein 2003; Guerra-Araiza et al. 2003).

vii. Kisspeptin and Kisspeptin Receptor: Kisspeptins are the natural ligands for GPR54. In humans and mice, inactivating mutations of GPR54 result in hypogonadotropic hypogonadism, indicating kisspeptins play a vital role in the regulation of GnRH1 secretion. In many species, centrally administered kisspeptins stimulate gonadotropin secretion in a GnRH1-dependant manner. Virtually all GnRH neurons coexpress GPR54 through which kisspeptin directly stimulates GnRH1 release (Messager 2005; Messager et al. 2005). In the hypothalamus, the vast majority of kisspeptin producing cells also express sex steroid receptors, particularly ERα. Thus, sex steroids are able to directly regulate the expression of Kiss1 mRNA, implicating kisspeptins as the 'missing link' between sex steroid feedback and GnRH1 secretion. Kiss1-expressing cells are localized to various regions of the forebrain in rodents, primates and sheep. In the arcuate nucleus (ARC) of the rodent and the ewe, sex steroids inhibit the expression of Kiss1 mRNA, suggesting that the kisspeptin secreting neurons here are the conduit for the negative feedback regulation of GnRH1 secretion. However, in the rodent anteroventral periventricular nucleus, sex steroids induce the expression of Kiss1, implying that these kisspeptin neurons play a role in the positive feedback regulation of GnRH1 secretion. Kisspeptin neurons in the

ARC appear well placed to play a role in the negative and positive feedback regulation of GnRH1 exerted by sex steroids (Smith 2008).

Further studies are warranted to define the exact spatio-temporal pattern of these axis components.

References

Alves S. E., McEwen B. S., Hayashi S., Korach K. S., Pfaff D. W. and Ogawa S. (2000) Estrogen-regulated progestin receptors are found in the midbrain raphe but not hippocampus of estrogen receptor alpha (ER alpha) gene-disrupted mice. *J Comp Neurol* 427, 185-195.

Badr M. and Pelletier G. (1987) Characterization and autoradiographic localization of LHRH receptors in the rat brain. *Synapse* 1, 567-571.

Badr M., Marchetti B. and Pelletier G. (1989) Changes in hippocampal LH-RH receptor density during maturation and aging in the rat. *Brain Res Dev Brain Res* 45, 179-184.

Bagshawe K. D., Orr A. H. and Rushworth A. G. (1968) Relationship between concentrations of human chorionic gonadotrophin in plasma and cerebrospinal fluid. *Nature* 217, 950-951.

Ban E., Crumeyrolle-Arias M., Latouche J., Leblanc P., Heurtier J. F., Drieu K., Fillion G. and Haour F. (1990) GnRH receptors in rat brain, pituitary and testis; modulation following surgical and gonadotropin-releasing hormone agonist-induced castration. *Mol Cell Endocrinol* 70, 99-107.

Barbaccia M. L. (2004) Neurosteroidogenesis: relevance to neurosteroid actions in brain and modulation by psychotropic drugs. *Crit Rev Neurobiol* 16, 67-74.

Barbaccia M. L., Serra M., Purdy R. H. and Biggio G. (2001) Stress and neuroactive steroids. *Int Rev Neurobiol* 46, 243-272.

Baulieu E. E. (1997) Neurosteroids: of the nervous system, by the nervous system, for the nervous system. *Recent Prog Horm Res* 52, 1-32.

Behl C. (2002) Estrogen can protect neurons: modes of action. *J Steroid Biochem Mol Biol* 83, 195-197.

Blaustein J. D. (2003) Progestin receptors: neuronal integrators of hormonal and environmental stimulation. *Ann N Y Acad Sci* 1007, 238-250.

Bowen R. L., Isley J. P. and Atkinson R. L. (2000) An association of elevated serum gonadotropin concentrations and Alzheimer disease? *J Neuroendocrinol* 12, 351-354.

Bowen R. L., Smith M. A., Harris P. L., Kubat Z., Martins R. N., Castellani R. J., Perry G. and Atwood C. S. (2002) Elevated luteinizing hormone expression colocalizes with neurons vulnerable to Alzheimer's disease pathology. *J Neurosci Res* 70, 514-518.

Bowen R. L., Verdile G., Liu T., Parlow A. F., Perry G., Smith M. A., Martins R. N. and Atwood C. S. (2004) Luteinizing hormone, a reproductive regulator that modulates the processing of amyloid-beta precursor protein and amyloid-beta deposition. *J Biol Chem* 279, 20539-20545.

Bukovsky A., Indrapichate K., Fujiwara H., Cekanova M., Ayala M. E., Dominguez R., Caudle M. R., Wimalsena J., Elder R. F., Copas P., Foster J. S., Fernando R. I., Henley D. C. and Upadhyaya N. B. (2003) Multiple luteinizing hormone receptor (LHR) protein variants, interspecies reactivity of anti-LHR mAb clone 3B5, subcellular localization of LHR in human placenta, pelvic floor and brain, and possible role for LHR in the development of abnormal pregnancy, pelvic floor disorders and Alzheimer's disease. *Reprod Biol Endocrinol* 1, 46.

Camacho-Arroyo I., Guerra-Araiza C. and Cerbon M. A. (1998) Progesterone receptor isoforms are differentially regulated by sex steroids in the rat forebrain. *Neuroreport* 9, 3993-3996.

Compagnone N. A. and Mellon S. H. (2000) Neurosteroids: biosynthesis and function of these novel neuromodulators. *Front Neuroendocrinol* 21, 1-56.

Crumeyrolle-Arias M., Latouche J., Laniece P., Charon Y., Tricoire H., Valentin L., Roux P., Mirambeau G., Leblanc P., Fillion G. and et al. (1994) "In situ" characterization of GnRH receptors: use of two radioimagers and comparison with quantitative autoradiography. *J Recept Res* 14, 251-265.

Dvorska I., Brust P., Hrbas P., Ruhle H. J., Barth T. and Ermisch A. (1992) On the blood-brain barrier to peptides: effects of immobilization stress on regional blood supply and accumulation of labelled peptides in the rat brain. *Endocr Regul* 26, 77-82.

Emanuele N., Anderson J., Andersen E., Connick E., Baker G., Kirsteins L. and Lawrence A. (1983) Extrahypothalamic brain luteinizing hormone: characterization by radioimmunoassay, chromatography, radioligand assay and bioassay. *Neuroendocrinology* 36, 254-260.

Fauconnier J. P., Teuwissen B. and Thomas K. (1978) Rate of disappearance in plasma of synthetic LH-RH intravenously injected in man. *Gynecol Obstet Invest* 9, 229-237.

Gao W. J. and Goldman-Rakic P. S. (2003) Selective modulation of excitatory and inhibitory microcircuits by dopamine. *Proc Natl Acad Sci U S A* 100, 2836-2841.

Granger A., Ngo-Muller V., Bleux C., Guigon C., Pincas H., Magre S., Daegelen D., Tixier-Vidal A., Counis R. and Laverriere J. N. (2004) The promoter of the rat gonadotropin-releasing hormone receptor gene directs the expression of the human placental alkaline phosphatase reporter gene in gonadotrope cells in the anterior pituitary gland as well as in multiple extrapituitary tissues. *Endocrinology* 145, 983-993.

Guerra-Araiza C., Villamar-Cruz O., Gonzalez-Arenas A., Chavira R. and Camacho-Arroyo I. (2003) Changes in progesterone receptor isoforms content in the rat brain during the oestrous cycle and after oestradiol and progesterone treatments. *J Neuroendocrinol* 15, 984-990.

Guerra-Araiza C., Reyna-Neyra A., Salazar A. M., Cerbon M. A., Morimoto S. and Camacho-Arroyo I. (2001) Progesterone receptor isoforms expression in the prepuberal and adult male rat brain. *Brain Res Bull* 54, 13-17.

Haour F., Dussaillant M., Leblanc P. and Rostene W. (1987) [Demonstration and topographical distribution of LHRH receptors in the central nervous system in the normal and castrated male rat]. *C R Acad Sci III* 305, 41-44.

Hogervorst E., Williams J., Budge M., Barnetson L., Combrinck M. and Smith A. D. (2001) Serum total testosterone is lower in men with Alzheimer's disease. *Neuroendocrinol Lett* 22, 163-168.

Hostetter G., Gallo R. and Brownfield M. (1981) Presence of immunoreactive luteinizing hormone in the rat forebrain. *Neuroendocrinology* 33, 241-245.

Jennes L., Dalati B. and Conn P. M. (1988) Distribution of gonadrotropin releasing hormone agonist binding sites in the rat central nervous system. *Brain Res* 452, 156-164.

Jennes L., McShane T., Brame B. and Centers A. (1996) Dynamic changes in gonadotropin releasing hormone receptor mRNA content in the mediobasal hypothalamus during the rat estrous cycle. *J Neuroendocrinol* 8, 275-281.

Jennes L., Eyigor O., Janovick J. A. and Conn P. M. (1997) Brain gonadotropin releasing hormone receptors: localization and regulation. *Recent Prog Horm Res* 52, 475-490; discussion 490-471.

Jennes L., Brame B., Centers A., Janovick J. A. and Conn P. M. (1995) Regulation of hippocampal gonadotropin releasing hormone (GnRH) receptor mRNA and GnRH-stimulated inositol phosphate production by gonadal steroid hormones. *Brain Res Mol Brain Res* 33, 104-110.

Kabbadj K., el-Etr M., Baulieu E. E. and Robel P. (1993) Pregnenolone metabolism in rodent embryonic neurons and astrocytes. *Glia* 7, 170-175.

Kim K. H., Patel L., Tobet S. A., King J. C., Rubin B. S. and Stopa E. G. (1999) Gonadotropin-releasing hormone immunoreactivity in the adult and fetal human olfactory system. *Brain Res* 826, 220-229.

Krichevsky A., Campbell-Acevedo E. A., Tong J. Y. and Acevedo H. F. (1995) Immunological detection of membrane-associated human luteinizing hormone correlates with gene expression in cultured human cancer and fetal cells. *Endocrinology* 136, 1034-1039.

Leblanc P., Crumeyrolle M., Latouche J., Jordan D., Fillion G., L'Heritier A., Kordon C., Dussaillant M., Rostene W. and Haour F. (1988) Characterization and distribution of receptors for gonadotropin-releasing hormone in the rat hippocampus. *Neuroendocrinology* 48, 482-488.

Lei Z. M. and Rao C. V. (1994) Novel presence of luteinizing hormone/human chorionic gonadotropin (hCG) receptors and the down-regulating action of hCG on gonadotropin-releasing hormone gene expression in immortalized hypothalamic GT1-7 neurons. *Mol Endocrinol* 8, 1111-1121.

Liu T., Wimalasena J., Bowen R. L. and Atwood C. S. (2007) Luteinizing hormone receptor mediates neuronal pregnenolone production via up-regulation of steroidogenic acute regulatory protein expression. *J Neurochem* 100, 1329-1339.

Lu F., Yang J. M., Wu J. N., Chen Y. C., Kao Y. H., Tung C. S. and Yang S. N. (1999) Activation of gonadotropin-releasing hormone receptors produces neuronal excitation in the rat hippocampus. *Chin J Physiol* 42, 67-71.

McEwen B. (2002) Estrogen actions throughout the brain. *Recent Prog Horm Res* 57, 357-384.

McEwen B. S. (1988) Genomic regulation of sexual behavior. *J Steroid Biochem* 30, 179-183.

Merchenthaler I., Gorcs T., Setalo G., Petrusz P. and Flerko B. (1984) Gonadotropin-releasing hormone (GnRH) neurons and pathways in the rat brain. *Cell Tissue Res* 237, 15-29.

Messager S. (2005) Kisspeptin and its receptor: new gatekeepers of puberty. *J Neuroendocrinol* 17, 687-688.

Messager S., Chatzidaki E. E., Ma D., Hendrick A. G., Zahn D., Dixon J., Thresher R. R., Malinge I., Lomet D., Carlton M. B., Colledge W. H., Caraty A. and Aparicio S. A. (2005) Kisspeptin directly stimulates gonadotropin-releasing hormone release via G protein-coupled receptor 54. *Proc Natl Acad Sci U S A* 102, 1761-1766.

Millar R. P., Lu Z. L., Pawson A. J., Flanagan C. A., Morgan K. and Maudsley S. R. (2004) Gonadotropin-releasing hormone receptors. *Endocr Rev* 25, 235-275.

Miller G. M. and Gibson M. J. (1994) Opioidergic modulation of N-methyl-D,L-aspartic-acid-stimulated LH release in young adult but not older male mice. *Neuroendocrinology* 59, 277-284.

Nunez J. L., Huppenbauer C. B., McAbee M. D., Juraska J. M. and DonCarlos L. L. (2003) Androgen receptor expression in the developing male and female rat visual and prefrontal cortex. *J Neurobiol* 56, 293-302.

Pierpaoli W. and Lesnikov V. (1997) Theoretical considerations on the nature of the pineal 'ageing clock'. *Gerontology* 43, 20-25.

Prange-Kiel J., Fester L., Zhou L., Lauke H., Carretero J. and Rune G. M. (2006) Inhibition of hippocampal estrogen synthesis causes region-specific downregulation of synaptic protein expression in hippocampal neurons. *Hippocampus* 16, 464-471.

Quanbeck C., Sherwood N. M., Millar R. P. and Terasawa E. (1997) Two populations of luteinizing hormone-releasing hormone neurons in the forebrain of the rhesus macaque during embryonic development. *J Comp Neurol* 380, 293-309.

Redding T. W., Kastin A. J., Gonzales-Barcena D., Coy D. H., Coy E. J., Schalch D. S. and Schally A. V. (1973) The half-life, metabolism and excretion of tritiated luteinizing hormone-releasing hormone (LH-RH) in man. *J Clin Endocrinol Metab* 37, 626-631.

Reed K. L., MacIntyre J. K., Tobet S. A., Trudeau V. L., MacEachern L., Rubin B. S. and Sower S. A. (2002) The spatial relationship of gamma-aminobutyric acid (GABA) neurons and gonadotropin-releasing hormone (GnRH) neurons in larval and adult sea lamprey, Petromyzon marinus. *Brain Behav Evol* 60, 1-12.

Reubi J. C. and Maurer R. (1984) Visualization of LHRH receptors in the rat brain. *Eur J Pharmacol* 106, 453-454.

Reubi J. C., Palacios J. M. and Maurer R. (1987) Specific luteinizing-hormone-releasing hormone receptor binding sites in hippocampus and pituitary: an autoradiographical study. *Neuroscience* 21, 847-856.

Schumacher M., Guennoun R., Robert F., Carelli C., Gago N., Ghoumari A., Gonzalez Deniselle M. C., Gonzalez S. L., Ibanez C., Labombarda F., Coirini H., Baulieu E. E. and De Nicola A. F. (2004) Local synthesis and dual actions of progesterone in the nervous system: neuroprotection and myelination. *Growth Horm IGF Res* 14 Suppl A, 18-33.

Sherwin B. B. (1999) Progestogens used in menopause. Side effects, mood and quality of life. *J Reprod Med* 44, 227-232.

Shima H., Fujisawa H., Suehiro E., Uetsuka S., Maekawa T. and Suzuki M. (2003) Mild hypothermia inhibits exogenous glutamate-induced increases in nitric oxide synthesis. *J Neurotrauma* 20, 1179-1187.

Short R. A., Bowen R. L., O'Brien P. C. and Graff-Radford N. R. (2001) Elevated gonadotropin levels in patients with Alzheimer disease. *Mayo Clin Proc* 76, 906-909.

Smith J. T. (2008) Kisspeptin signalling in the brain: Steroid regulation in the rodent and ewe. *Brain Res Rev* 57, 288-298.

Thompson T. L. and Moss R. L. (1992) Specific binding of 125I-LHRH agonist to hippocampal membranes: fluctuations during the estrous cycle. *Peptides* 13, 891-896.

Tobet S. A., Hanna I. K. and Schwarting G. A. (1996) Migration of neurons containing gonadotropin releasing hormone (GnRH) in slices from embryonic nasal compartment and forebrain. *Brain Res Dev Brain Res* 97, 287-292.

Vadakkadath Meethal S. and Atwood C. S. (2005) The role of hypothalamic-pituitary-gonadal hormones in the normal structure and functioning of the brain. *Cell Mol Life Sci* 62, 257-270.

Veiga S., Garcia-Segura L. M. and Azcoitia I. (2004) [The neuroprotective properties of sex steroids and neurosteroids]. *Rev Neurol* 39, 1043-1051.

Whitfield G. K. and Kourides I. A. (1985) Expression of chorionic gonadotropin alpha- and beta-genes in normal and neoplastic human tissues: relationship to deoxyribonucleic acid structure. *Endocrinology* 117, 231-236.

Wilson A. C., Salamat M. S., Haasl R. J., Roche K. M., Karande A., Meethal S. V., Terasawa E., Bowen R. L. and Atwood C. S. (2006) Human neurons express type I GnRH receptor and respond to GnRH I by increasing luteinizing hormone expression. *J Endocrinol* 191, 651-663.

Yokotani T., Koizumi T., Taniguchi R., Nakagawa T., Isobe T., Yoshimura M., Tsubota N., Hasegawa K., Ohsawa N., Baba S., Yasui H. and Nishimura R. (1997) Expression of alpha and beta genes of human chorionic gonadotropin in lung cancer. *Int J Cancer* 71, 539-544.

Zhang F. P., Hamalainen T., Kaipia A., Pakarinen P. and Huhtaniemi I. (1994) Ontogeny of luteinizing hormone receptor gene expression in the rat testis. *Endocrinology* 134, 2206-2213.